In the Claims

1-35 (canceled).

36 (new). A composition of matter comprising:

(a) an isolated antibody that induces superagonistic signaling by a cell surface receptor, wherein said antibody binds to the extracellular portion of the receptor at a membrane proximal region and said receptor comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase, wherein said antibody does not bind only the C'-D loop of human CD28;

(b) an isolated chimeric protein that induces superagonistic signaling by a cell surface receptor, which chimeric protein comprises: (i) an amino acid sequence comprising a fragment of a ligand of the receptor, or a homologue of such a fragment, wherein the fragment or homologue is capable of binding to the extracellular portion of the receptor at a membrane proximal region, and (ii) an Fc region of an antibody, wherein said receptor comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase;

(c) an isolated chimeric protein that induces superagonistic signaling by one or two types of cell surface receptor, said chimeric protein comprising two Fv regions of an antibody that may be the same or different, wherein at least one of the Fv regions is capable of binding to a first receptor, and the other Fv region either binds to (i) said first receptor, or (ii) a second type of cell surface receptor which is found on a cell that contacts a cell which expresses said first receptor, wherein said first receptor, and optionally also said second receptor, comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase;

(d) an isolated peptide of 5 to 20 amino acids comprising a sequence that binds to an antibody that:

(A) that induces superagonistic signaling by a cell surface receptor, wherein said antibody binds to the extracellular portion of the receptor at a membrane proximal region and said receptor comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase, wherein said antibody does not bind

only the C'-D loop of human CD28;

(B) an isolated chimeric protein that induces superagonistic signaling by a cell surface receptor, which chimeric protein comprises: (i) an amino acid sequence comprising a fragment of a ligand of the receptor, or a homologue of such a fragment, wherein the fragment or homologue is capable of binding to the extracellular portion of the receptor at a membrane proximal region, and (ii) an Fc region of an antibody, wherein said receptor comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase; or

(C) an isolated chimeric protein that induces superagonistic signaling by one or two types of cell surface receptor, said chimeric protein comprising two Fv regions of an antibody that may be the same or different, wherein at least one of the Fv regions is capable of binding to a first receptor, and the other Fv region either binds to (i) said first receptor, or (ii) a second type of cell surface receptor which is found on a cell that contacts a cell which expresses said first receptor, wherein said first receptor, and optionally also said second receptor, comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase;

(e) a crystal comprising (i) CD28; (ii) a fragment of CD28; or (iii) a homologue of CD28 or a fragment thereof;

(f) a crystal comprising a CD28 specific antibody or an antigen binding fragment of said antibody bound to: (i) CD28; (ii) a fragment of CD28; or (iii) a homologue of CD28 or a fragment of thereof;

(g) a crystal having the structural coordinates shown in Table 4;

(h) machine-readable data storage medium comprising a data storage material encoded with a machine readable data which when read by an appropriate machine displays a representation of a crystal:

(A) comprising (i) CD28; (ii) a fragment of CD28; or (iii) a homologue of CD28 or a fragment thereof;

(B) comprising a CD28 specific antibody or a fragment of said antibody bound to:(i) CD28; (ii) a fragment of CD28; or (iii) a homologue of CD28 or a fragment thereof; or

(C) having the structural coordinates shown in Table 4; or

(i) a computer program product comprising a program code means stored on a computer readable storage medium for comparing a structural model of a candidate modulator with a structural model of CD28 to thereby determine whether the modulator will bind to CD28, wherein the structural model is derived from, or comprises, structural coordinates of a crystal of: (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a fragment of CD28.

37 (new). The composition of matter according to claim 36, wherein said antibody or chimeric protein:

(i) binds orthogonally to the main axis of the domain of the receptor which it is binding; and/or

(ii) lies parallel to the cell surface when bound to the receptor; and/or

(iii) binds to a β-strand polypeptide chain of the receptor; and/or

(iv) binds within 75Å of the cell surface.

38 (new). The composition of matter according to claim 36, wherein said antibody or chimeric protein binds to a sequence as shown in Table 1 or an equivalent homologous sequence in the proximal membrane region of a receptor which is capable of being induced to signal by the antibody or chimeric protein.

39 (new). The composition of matter according to claim 37, wherein said antibody or chimeric protein binds to a sequence as shown in Table 1 or an equivalent homologous sequence in the proximal membrane region of a receptor which is capable of being induced to signal by the antibody or chimeric protein.

40 (new). The composition of matter according to claim 36, wherein said receptor

(i) comprises an ITAM motif, ITIM motif or "switch" signaling motif; and/or

(ii) is a member of the CD28 family of proteins; and/or

(iii) is expressed on the surface of a cell of the immune system; and/or

(iv) comprises a cytoplasmic domain capable of being phosphorylated by a Src kinase; and/or

(v) comprises a cytoplasmic domain capable of being dephosphorylated by CD45; and/or

(vi) is one of the receptors listed in Table 2, or is a homologue thereof.

41 (new). The composition of matter according to claim 37, wherein said receptor

(i) comprises an ITAM motif, ITIM motif or "switch" signaling motif; and/or

(ii) is a member of the CD28 family of proteins; and/or

(iii) is expressed on the surface of a cell of the immune system; and/or

(iv) comprises a cytoplasmic domain capable of being phosphorylated by a Src kinase; and/or

(v) comprises a cytoplasmic domain capable of being dephosphorylated by CD45; and/or

(vi) is one of the receptors listed in Table 2, or is a homologue thereof.

42 (new). The composition of matter according to claim 38, wherein said receptor

(i) comprises an ITAM motif, ITIM motif or "switch" signaling motif; and/or

(ii) is a member of the CD28 family of proteins; and/or

(iii) is expressed on the surface of a cell of the immune system; and/or

(iv) comprises a cytoplasmic domain capable of being phosphorylated by a Src kinase; and/or

(v) comprises a cytoplasmic domain capable of being dephosphorylated by CD45; and/or

(vi) is one of the receptors listed in Table 2, or is a homologue thereof.

43 (new). The composition of matter according to claim 39, wherein said receptor

(i) comprises an ITAM motif, ITIM motif or "switch" signaling motif; and/or

(ii) is a member of the CD28 family of proteins; and/or

(iii) is expressed on the surface of a cell of the immune system; and/or

(iv) comprises a cytoplasmic domain capable of being phosphorylated by a Src kinase; and/or

(v) comprises a cytoplasmic domain capable of being dephosphorylated by CD45; and/or

(vi) is one of the receptors listed in Table 2, or is a homologue thereof.

44 (new). A method of identifying a candidate modulator or a candidate agent that modulates a receptor comprising:

A) determining whether a candidate agent binds to a membrane proximal extracellular region of the receptor, to thereby determine whether the candidate agent is capable of superagonizing the receptor; or

B) identifying a modulator of CD28 comprising comparing a structural model of a candidate modulator with a structural model of CD28 to thereby determine whether the modulator will bind to CD28, wherein the structural model is derived from, or comprises, structural coordinates of a crystal of: (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a homologue of a fragment of CD28;

wherein said receptor (i)comprises an ITAM motif, ITIM motif or "switch" signaling motif, and/or (ii) is a member of the CD28 family of proteins, and/or (iii) is expressed on the surface of a cell of the immune system, and/or (iv) comprises a cytoplasmic domain capable of being phosphorylated by a Src kinase, and/or (v) comprises a cytoplasmic domain capable of being dephosphorylated by CD45, and/or (vi) is one of the receptors listed in Table 2, or is a homologue thereof and/or (vii) comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase.

45 (new). The method according to claim 44, wherein said method comprises determining whether a candidate agent which binds to the receptor or fails to bind to a mutated version of the receptor wherein one or more amino acids in a membrane proximal extracellular

region of the receptor have been mutated, said failure to bind to the mutant receptor indicating that the agent is capable of inducing superagonistic signaling by the receptor.

46 (new). The method according to claim 45, wherein the method is performed by contacting the candidate agent with (i) a full length receptor with said mutations, or (ii) a homologue of a full length receptor with said mutations, or (iii) a fragment of (i) or (ii) comprising said mutations.

47 (new). The method according to claim 44, wherein the location of the binding of the candidate agent is determined by contacting the candidate agent with: (i) a peptide comprising sequence from a membrane proximal extracellular region of the receptor that is at least five amino acids in length; or (ii) an array of overlapping peptides that represent fragments of the receptor and are 5 to 20 amino acids in length and determining whether the candidate agent binds to the peptide or a peptide in the array of overlapping peptides, the binding of the candidate agent to a peptide indicating that the agent is capable of inducing superagonistic signaling of said receptor.

48 (new). The method according to claim 44, wherein said candidate agent is an antibody.

49 (new). The method according to claim 44, wherein said comparison comprises fitting (docking) the structural model of the candidate modulator with the structural model of CD28, and optionally determining the binding free energy of binding between the candidate modulator and CD28, wherein a low (more negative) binding free energy indicates that the candidate is likely to bind to CD28.

50 (new). The method according to claim 49, wherein the binding free energy is calculated by (i) summing the free energies of interatomic contacts between the structural model of the candidate modulator and the structural model of CD28, or (ii) determining the free binding energy between the force field of the candidate modulator and the force field of CD28.

51 (new). The method according to claim 44, wherein determining whether or not the candidate modulator binds to CD28 comprises: (i) comparing the fitting of the structural model of the candidate modulator and the structural model of CD28 with the fitting of a structural model of another protein bound to a ligand, to thereby determine whether or not the candidate modulator will bind to CD28; or (ii) comparing the fitting of the structural model of the candidate modulator and the structural model of CD28 with the fitting of a structural model of another protein bound to a ligand, to thereby determine whether or not the candidate modulator will bind to CD28, wherein the structural coordinates are obtainable by subjecting a crystal of (A) CD28, (B) a fragment of CD28, or (C) a homologue of (A) or (B), to X-ray diffraction measurements and deducing the structural coordinates from the diffraction measurements.

52 (new). The method according to claim 44, wherein: A) the crystal is: i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a homologue of a fragment of CD28 bound to a CD28 specific antibody or an antigen binding fragment of said antibody ; or (ii) the crystal has the structural coordinates shown in Table 4.

53 (new). The method according to claim 44, further comprising contacting the identified modulator of CD28 with (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a fragment thereof to determine whether or not the modulator is capable of binding, or modulating the activity of CD28.

54 (new). A method of making a crystal comprising providing a solution that comprises (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a fragment thereof, and optionally a CD28 specific antibody or an antigen binding fragment of said antibody, and subjecting the solution to conditions that cause the crystal to form.

55 (new). The method according to claim 54, comprising:

(a) expressing (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a fragment thereof in the form of a fusion protein with a second protein that is able to form a homodimer, wherein the presence of the second protein in the fusion protein causes (i), (ii) or (iii) to dimerize;

(b) cleaving the second protein from the fusion protein;

(c) reducing and alkylating one or more of the disulphide bonds present in the stalk-like region of (i), (ii) or (iii); and

(d) crystallizing (i), (ii) or (iii) bound to a Fab fragment of an antibody.

56 (new). The method according to claim 55, wherein the second protein mentioned in step (b) is an Fc fragment of an antibody.

57 (new). The method according to claim 54, wherein prior to crystallization (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a fragment thereof is expressed in the form of a fusion protein with an Fc fragment of an antibody, and optionally (i), (ii) or (iii) is cleaved from the fusion protein by thrombin.

58 (new). The method according to claim 54, wherein the (i) CD28, (ii) a fragment of CD28, or (iii) a homologue of CD28 or a fragment thereof is present in monomeric form in the crystal and/or one or more cysteine residues in the stalk-like region of (i), (ii) or (iii) are ethylated in the crystal.

59 (new). A method of modulating the immune response of a patient or of inducing superagonistic signaling by a receptor comprising:

(i) administering a modulator of CD28 to said patient; or

(ii) administering an antibody or chimeric protein that induces superagonistic signaling by a cell surface receptor, wherein said antibody or chimeric protein binds to the extracellular portion of the receptor at a membrane proximal region and said receptor

comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase, wherein said antibody or chimeric protein does not bind only the C'-D loop of human CD28 to said patient; or

(iii) administering an agent that binds to a membrane proximal extracellular region of the receptor and has the ability to superagonize the receptor to said patient; or

(iv) administering a peptide that stimulates an antibody response in the patient wherein the antibody binds to the extracellular portion of the receptor at a membrane proximal region and said receptor comprises a cytoplasmic domain which is dependent on an extrinsic protein kinase and wherein said antibody does not bind only the C'-D loop of human CD28; or

(v) administering a nucleic acid capable of expressing (i), (ii), (iii) or (iv) to said patient; or

(vi) administering an agent or modulator to a patient that sterically inhibits contact between a phosphatase of the cell and the receptor, excluding a method in which an antibody that binds only the C'-D loop of CD28 is used to sterically inhibit contact between CD28 and the phosphatase CD45.

60 (new). A method of obtaining a superagonistic antibody comprising:

(i) screening antibodies for the ability to induce superagonistic signaling by a receptor wherein said antibodies have been obtained by immunizing an animal with (a) said receptor, (b) a homologue of said receptor, or (c) a fragment of (a) or (b); or

(ii) screening antibodies for the ability to induce superagonistic signaling by a receptor, wherein said antibodies have been generated in a combinatorial antibody library.

61 (new). The method according to claim 60, wherein said method comprises:

(i) immunizing an animal with a peptide comprising a sequence of length 5 to 20 amino acids which represents an extracellular membrane proximal region of the receptor and obtaining the antibody produced by the animal against said sequence; or

(ii) selecting an antibody from a combinatorial antibody library based on its ability to bind a peptide comprising 5 to 20 amino acids of represents an extracellular membrane proximal region of the receptor; and optionally

(iii) recombinantly expressing the antibody obtained in (i) or (ii).